REMARKS

Claims 15-55 are currently pending. Claims 15, 20-24, 38, 46 and 55 have been amended in this action.

The invention

Applicants have invented diagnostic test kits and probes for hybridization, or for use as primers for determining mutations, especially deletions of relatively large stretches of nucleotides in genes associated with hereditary types of cancer, particularly in the BRCA1 gene. The probes are complementary to at least one stretch of nucleotides of the target gene in the sense or the anti-sense direction and may be used in various detection methods, such as hybridization or polymerase chain reaction (PCR) methods.

The probes may flank one or both sides of a deletion and in certain embodiments may comprise a fusion of two sequences adjacent to the site of a deletion of a stretch of nucleotides, such as for instance, between two ALU-elements of the BRCA1 gene.

The probes of the invention are useful for detecting the presence of breast cancer and for detecting predisposition for breast cancer. In particular, the probes may be used in the detection of deletions that cause frame shift mutations, termination mutations or deletions of a stretch of nucleotides between two ALU-elements.

Finally, the invention also provides a method for determining the presence of a deletion of a stretch of nucleotides derived from the BRCA1 gene in a sample by contacting a

sample with at least one probe which alone or together with a second means for detecting a deletion within the BRCA1 gene, allowing hybridization to occur and detecting the hybridization product.

The rejection under 35 U.S.C. §112 raised in the Office Action of October 29, 2001

In the office action of October 29, 2001 the Examiner recited a single ground of rejection based on 35 U.S.C. §112, second paragraph which is addressed below.

Claims 15-55 were rejected as allegedly containing subject matter which was not described in such a way in the specification as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the invention.

According to the Examiner, the specification fails to meet the requirements of §112, first paragraph as set forth in *Vas Cath Inc. v. Mahurkar,* 19 USPQ2d 1111, which holds that the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date the Applicant was in possession of the claimed invention. The Examiner maintains that absent a written description disclosing a deletion of a major part or all of exons 14, 15 and 16 in the BRCA1 gene as claimed in claims 15-55, the specification fails to show that Applicant was in fact in possession of the claimed invention at the time the application for patent was filed.

Applicants believe that the specification adequately teaches deletions in exons 13, 14, 15, 16 or at least a major part of exon 22 of the BRCA1 gene to convince one of ordinary

skill that the inventors were in possession of the invention relating to each of these deletions as recited in claims 15-55 before amendment.

However, in the interest of obtaining an early allowance of claims in the present application and without prejudice to prosecution of the broader embodiments in a continuation application, Applicants have amended claim 15 to recite:

"A diagnostic test kit...wherein a means is provided for detecting a deletion of...a BRCA1 gene..., wherein said deletion comprises at least a major part of exon 13, at least a major part of exon 22, or both."

Similarly, claims 20-24 to kits according to claim 15, have been amended to recite:

"..., wherein the deletion comprises all of exon 13, all of exon 22, or all of both exon 13 and exon 22 of the BRCA1 gene."

Likewise, claims 38 and 46, drawn to probes for use in diagnostic test kits, have been amended to recite the same limitation to deletions comprising all of exon 13, all of exon 22, or all of both exon 13 and exon 22 of the BRCA1 gene.

Finally, claim 55, drawn to a method of determining the presence of a deletion in a nucleic acid sample derived from a BRCA1 gene having a deletion, has been amended to recite the identical limitation as in the above amended claims.

Support for amendments to claims 15-55

Claims 15, 20-24, 38, 46 and 55 as amended are supported by the specification as originally filed. The amendments are supported *inter alia* by the specification at page 7 at lines 1-13 and page 9, lines 6-20 and by the Examples (initially entitled "Experimental part.") as filed. No new matter has been added by these amendments.

Entry of the present Amendment and reconsideration of the single outstanding rejection is respectfully requested. Applicants believe that the pending claims15-55 as amended are now in condition for allowance, which action is earnestly solicited.

If the Examiner has any questions relating to this Amendment or to this application in general, the Examiner is respectfully invited to contact the Applicants' attorney at the telephone number provided below.

Respectfully submitted,

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VERSION OF AMENDMENT WITH MARKINGS TO SHOW CHANGES MADE

In the specification

At page 13, line 6, delete "**Experimental part.**" and insert in its place:

-- **EXAMPLES.** --

In the claims:

Please amend claims 15, 20-24, 38, 46 and 55 as follows:

(All the pending claims, 15-55 are reproduced for the Examiner's convenience)

15. (Amended) A diagnostic test kit for detecting the presence of or predisposition for breast cancer, wherein a means is provided for detecting a deletion of a stretch of nucleotides from a BRCA1 gene in a sample, wherein said deletion comprises at least a major part of ~~any one or all of exons 13, 14, 15 and16, or at least a major part of exon 22~~ exon 13, at least a major part of exon 22, or both.

16. A diagnostic test kit according to claim 15, wherein the means comprises at least one probe for hybridization.

17. A diagnostic test kit according to claim 15, wherein the means comprises the necessary elements for Southern blotting.

18. A diagnostic test kit according to claim 16, wherein the probe comprises a sequence complementary to sequences on both sides of the deletion in the BRCA1 gene.

19. A diagnostic test kit according to claim 17, wherein the necessary elements for Southern blotting comprises a probe, the probe comprising a sequence complementary to sequences on both sides of the deletion in the BRCA1 gene.

20. (Amended) A diagnostic test kit according to claim 15, wherein the deletion comprises all of ~~one or more of exons 13, 14, 15, 16 or 22~~ exon 13, all of exon 22, or all of both exon 13 and exon 22 of the BRCA1 gene.

21. (Amended) A diagnostic test kit according to claim 16, wherein the deletion comprises all of ~~one or more of exons 13, 14, 15, 16 or 22~~ exon 13, all of exon 22, or all of both exon 13 and exon 22 of the BRCA1 gene.

22. (Amended) A diagnostic test kit according to claim 17, wherein the deletion comprises all of ~~one or more of exons 13, 14, 15, 16 or 22~~ exon 13, all of exon 22, or all of both exon 13 and exon 22 of the BRCA1 gene.

23. (Amended) A diagnostic test kit according to claim 18, wherein the deletion comprises all of ~~one or more of exons 13, 14, 15, 16 or 22~~ exon 13, all of exon 22, or all of both exon 13 and exon 22 of the BRCA1 gene.

24. (Amended) A diagnostic test kit according to claim 19, wherein the deletion comprises all of ~~one or more of exons 13, 14, 15, 16 or 22~~ exon 13, all of exon 22, or all of both exon 13 and exon 22 of the BRCA1 gene.

25. A diagnostic test kit according to claim 15, wherein the deletion comprises a frame shift and/or a termination codon.

26. A diagnostic test kit according to claim 16, wherein the deletion comprises a frame shift and/or a termination codon.

27. A diagnostic test kit according to claim 17, wherein the deletion comprises a frame shift and/or a termination codon.

28. A diagnostic test kit according to claim 18, wherein the deletion comprises a frame shift and/or a termination codon.

29. A diagnostic test kit according to claim 19, wherein the deletion comprises a frame shift and/or a termination codon.

30. A diagnostic test kit according to claim 20, wherein the deletion comprises a frame shift and/or a termination codon.

31. A diagnostic test kit according to claim 15, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

32. A diagnostic test kit according to claim 16, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

33. A diagnostic test kit according to claim 17, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

34. A diagnostic test kit according to claim 18, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

35. A diagnostic test kit according to claim 19, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

36. A diagnostic test kit according to claim 20, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

37. A diagnostic test kit according to claim 25, wherein the deletion comprises a deletion of a stretch of nucleotides between two ALU-elements.

38. (Amended) A probe for use in a diagnostic test kit for detecting the presence of or predisposition for breast cancer, wherein a means is provided for detecting a deletion of a stretch of nucleotides from a BRCA1 gene in a sample, and wherein said deletion comprises at least a major part of ~~an, one or all of exons 13, 14, 15 and16, or at least a major part of exon 22~~ exon 13, at least a major part of exon 22, or both; said probe comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

39. A probe for use in a diagnostic test kit according to claim 38, wherein the means comprises at least one probe for hybridization, the probe comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

40. A probe for use in a diagnostic test kit according to claim 38, wherein the means comprises the necessary elements for Southern blotting, comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

41. A probe for use in a diagnostic test kit according to claim 18, comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

42. A probe for use in a diagnostic test kit according to claim 19 comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

43. A probe for use in a diagnostic test kit according to claim 20 comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

44. A probe for use in a diagnostic test kit according to claim 25 comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

45. A probe for use in a diagnostic test kit according to claim 31 comprising a nucleotide sequence which is a fusion of two ALU elements of the BRCA1 gene.

46. (Amended) A probe for use in a diagnostic test kit according to claim 15, wherein said deletion comprises at least a major part of ~~any one or all of exons 13, 14, 15 and16, or at least a major part of exon 22~~ exon 13, at least a major part of exon 22, or both, and wherein the probe comprises ~~is~~ a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

47. A probe for use in a diagnostic test kit according to claim 16, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

48. A probe for use in a diagnostic test kit according to claim 17, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

49. A probe for use in a diagnostic test kit according to claim 18, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

50. A probe for use in a diagnostic test kit according to claim 19, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

51. A probe for use in a diagnostic test kit according to claim 20, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

52. A probe for use in a diagnostic test kit according to claim 25, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

53. A probe for use in a diagnostic test kit according to claim 31, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

54. A probe for use in a diagnostic test kit according to claim 38, which is a fusion product of two sequences adjacent to the site of a deletion of a stretch of nucleotides.

55. (Amended) A method of determining the presence in a sample of a nucleic acid derived from a BRCA1 gene having a deletion of a stretch of nucleotides, comprising contacting said sample with at least one probe which alone or together with a second means for detecting said deletion of a stretch of nucleotides from a BRCA1 gene, distinguishes between BRCA1 genes having said deletion and BRCA1 genes not having said deletion, allowing hybridization between said probe and said nucleic acids to form a hybridization product and identifying the hybridization product, wherein said deletion comprises at least a major part of ~~any one or all of exons 13, 14, 15 and16, or at least a major part of exon 22~~ exon 13, at least a major part of exon 22, or both.